REMARKS

Claims 1, 4, 7, 8, and 10-27 presently appear in this case. No claims have been allowed. The official action of May 3, 2007, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method of treating a malignant tumor, which has an operative retinoblastoma (RB) protein, in a subject by administering a composition that causes a decrease in the $[GSH]^2/[GSSG]$ ratio in the malignant cells of the tumor. The amounts of the composition and the mode of administration are such that the decreased ratio is reached and maintained in the malignant cells continuously for about 15 to about 75 hours. Preferably, the agents in the composition are selected from agents that cause oxidation of GSH, agents that cause formation of an adduct or a conjugate with GSH, agents that cause inhibition of the GCS enzyme, and agents that cause inhibition of the GR enzyme.

Claims 1, 4, 7, 10, 12, 14-20 and 24 have been rejected under 35 U.S.C. 112, first paragraph. The examiner states that while applicants have written description for the general class of agents recited in the claims, they do not have adequate written description for a "precursor" of such agents. This rejection is respectfully traversed.

A precursor is a compound that generates the active compound *in vivo* (see, for example, page 14, line 19, of the present specification). Thus, it does not matter if the biologically active compound is administered or another compound is administered that causes the biologically active compound to be formed *in vivo*. Nevertheless, in order to avoid use of the term "precursor," to which the examiner objects, the claims have been amended to refer to, for example, "an agent that causes oxidation of GSH" rather than "an agent that oxidizes GSH." This clarifies the general class of agents that the examiner agrees have written description, without using the term precursor. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 1, 4, 7, 8, 10-21 and 24 have been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of tumors with disulfiram, BSO and carmustine, does not reasonably provide enablement for the treatment of tumors with the broad genera of agents contemplated by the instant claims. The examiner states that the specification must teach those of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. The examiner states that determining if any particular claimed

compound or combination of compounds would treat any particular malignant tumor would require synthesis of the compound, formulation into a suitable dosage form and subjecting it to clinical trial or to testing in an assay known to correlate to clinical efficacy of such treatment. The examiner states that this is undue experimentation given the limited guidance and direction provided by the applicants. This rejection is respectfully traversed.

The present invention is not directed to novel compounds. Thus, the examiner's statement that the practice of the invention would require synthesis of compounds and formulation into suitable dosage forms is not entirely accurate. The present invention uses known classes of compounds, but uses them in a novel combination and administering them with a novel protocol in order to obtain the unexpected results of the present invention. Thus, for example, one of ordinary skill in the art seeking to practice the present invention would not need to discover what compounds cause oxidation of GSH. This is a known class of compounds and those of ordinary skill in the art are in possession of this class of compounds without any experimentation. The same is true with all of the other classes of compounds that may be used in the present invention.

The present invention is based on the inventor's discovery that manipulating the intracellular redox potential, *E*, can selectively kill cancer cells. If *E* is above a threshold, θ, then a proliferating cell becomes arrested in phase G_{1pm}. If *E* is maintained above θ for the default time, then all cancer cells that have been in G_{1pm} from the time *E* rose above θ will undergo apoptosis, while normal cells will take refuge in the quiescent stage G_0 (see, for example, page 3, lines 12-28, of the present specification; see also page 12, lines 20-29). If *E* in a cancer cell is maintained above θ for the cell-cycled period plus the default time, then the cell will undergo apoptosis, regardless of the cell-cycle phase it was in when *E* first rose. This is why it is important that the decreased $[GSH]^2/[GSSG]$ ratio be reached and maintained in the malignant cells continuously for about 15 to about 75 hours.

Thus, if only an oxidizing agent is used, *E* will rapidly rise as GSH is oxidized to GSSG, (thereby decreasing the $[GSH]^2/[GSSG]$ ratio) but *E* will rapidly fall back to its original value as electrons are transferred back via the enzyme glutathione reductase, GR, from NADPH. Thus, if only an oxidizing agent is used, the maintenance of an elevated *E* for tens of hours requires continuous administration of the oxidizing agent, which could reach several grams daily (see

the paragraph bridging pages 16 and 17 of the present specification). While this is not a preferred embodiment, those of ordinary skill in the art would understand that if a GSH oxidant is the only compound being administered, it must be administered in such a way as to maintain an increased *E* (meaning a decreased $[GSH]^2/[GSSG]$ ratio) for 15 to 75 hours, which will require continuous administration in the required amounts.

By adding a second agent, such as carmustine, at a concentration that does not kill cells but that prevents GSH restoration by inhibiting the GR, the GSSG cannot be reduced back to GSH. Thus, *E* will remain high until there is more *de novo* synthesis of GR (see the paragraph bridging pages 17 and 18 of the present specification). Once one of ordinary skill in the art understands the theory of the present invention, it would not take undue experimentation to determine operable combinations of the classes of compounds disclosed in the specification and optimum means of administration in order to maintain the reduced levels of *E* for the necessary time period. It should be noted that the administration protocols are intended to maintain the reduced ratio for the necessary time period. This does not mean that the cells will necessarily be in contact with the agents for this length of time. Note the present specification in the paragraph

bridging pages 11 and 12. The effective contact time can be much longer than the actual contact time. Thus, the preferred combination of the present invention effectively serves to increase and maintain *E* high enough to induce apoptosis, even for several hours after the agents are gone. The *in vivo* results discussed below confirm the usefulness of the present invention. A decrease in the rate of tumor growth is useful in extending the life of cancer patients with relatively slow growing tumors, which are the most difficult to treat.

As the examiner recognizes, the level of skill in the art is very high. Indeed, it is higher than that indicated by the examiner. The present invention is not directed to any physician with a few years experience; it is directed to physicians or Ph.D.'s who have experience in drug formulation and pharmacology for whom it would not be undue experimentation to determine other operable combinations of the classes of compounds disclosed herein and appropriate protocols of administration in order to obtain the ultimate result that is desired with respect to $[GSH]^2/[GSSG]$ concentration.

The examiner also questions whether the present invention can lead to effective treatment of all malignant tumors. The mechanism of the present invention requires an operative RB protein, i.e., one capable of phosphorylation.

See page 2, line 24, through page 3, line 28, and page 14, lines 1-2. See also Scheme 1 on page 40 of the specification. Accordingly, the claims have now been amended to specify that the tumors are ones with an operative RB protein.

To date, the present invention has been tested with respect to MX-1 breast cancer cells, MBT bladder tumor cells, DU-145 human prostate cancer cells, BXPC3, Colo and PAN 10.5 pancreatic cancer cells, and U87 and A172 glioma cells. *In vivo* tests have also been conducted with MX-1 and MBT cells. Attached hereto are executed declarations of Lee M. Spetner and Arnold Hoffman, and an unexecuted declaration of Sanford R. Sampson, detailing the results of these tests and showing the feasibility of the concept of the present invention with many diverse examples of malignant tumor cells. An executed copy of the Sampson declaration will follow shortly with a supplemental response. A declaration relating to the glioma cell tests will also follow with a supplemental response. These tests are predictive of *in vivo* operability over a wide range of malignancies. With all of this evidence, one of ordinary skill in the art would not find to be incredible the statement in the present specification that the concept of inducing apoptosis by continuously maintaining cancer cells in the G_{1pm} state until programmed cell death kicks in is a strategy that will work for any malignant cells with an

operative RB protein, as all malignant cells have the property of being unable to enter G_0.

Also included in the Sampson Declaration is an experiment with 3T3 non-malignant cells showing that the same treatment will suspend proliferation, but will not kill the cells. Thus, the present invention is selectively effective on malignant cells. This evidence should be sufficient to establish that those of ordinary skill in the art would expect the present invention to work with respect to all malignant tumors that have an operative RB protein, and that the invention can be practiced by those of ordinary skill in the art without undue experimentation. Variations of reagents are also disclosed. For all of these reasons reconsideration and withdrawal of this rejection are respectfully urged.

Claims 1, 4, 7, 8 and 10-25 have been rejected under 35 U.S.C. 102(a), as being anticipated by Hoffman (WO02/056823). The examiner states that practicing the invention of Hoffman will inherently cause a $[GSH]^2/[GSSG]$ to be maintained at a reduced state for 15 to 75 hours. This rejection is respectfully traversed.

The Hoffman PCT publication is not available as a reference under 35 U.S.C. 102(a) as it is not the invention of another. Attached hereto is a declaration signed by the present inventors clarifying that the inventive entity named

in the PCT application was erroneous and has been corrected by the filing of the present CIP application. This correction of inventorship declaration establishes that the inventorship of both applications are identical, and thus the Hoffman PCT publication is not available as a reference. Accordingly, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 1, 4, 7, 8 and 10-25 have been rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. patent 6,589,987 to Kennedy in view of Huang, Ali-Osman and Nagendra. The examiner states that Kennedy discloses that disulfiram inhibits the growth of cancer cells and can be administered in combination with another anticancer agent, and that Huang discloses that the GSH level in hepatocytes increases during active proliferation and that BSO treatment decreased GSH levels and rates of growth. The examiner states that Ali-Osman discloses that depletion of GSH by BSO in human malignant glioma cells potentiated the cytotoxicity of BCNU (carmustine). The examiner recognizes that Ali-Osman discloses that BSO has no effect on cell survival, but sensitizes the cell to treatment with BCNU. The examiner states that Nagendra discloses that chronic administration of disulfiram affects GSH metabolism, thus inducing oxidative stress on the brain. The examiner considers it obvious to

administer a multiplicity of such agents that would be effective in the treatment of cancer. The examiner states that in both the prior art and the present claims, the ultimate treatment of tumors is or would have been expected and that the active ingredients would be administered in effective amounts to treat cancer and/or tumors. The examiner states that modifying administration regimes, doses, length of administration, etc., in order to elicit optimal treatment of tumors are well within the purview of the skilled artisan. This rejection is respectfully traversed.

While Kennedy discloses administration of disulfiram so as to inhibit the growth of cancer cells, it explicitly states in Example 6 that disulfiram does not decrease proliferation through redox mechanisms. Thus, no one reading Kennedy would learn anything about the present invention.

Huang discloses that the addition of BSO to human hepatocellular carcinoma cells decreases GSH levels and rates of growth. DNA synthesis in BSO treated cells was lower than controls. Huang hypothesizes, as an alternative hypothesis, that an increase in the cellular GSH content may change the thiol-redox status of a cell, which may then affect the expression or activity of factors important for cell-cycle progression. However, Huang does not teach that BSO would be useful as an anticancer agent. Furthermore, the discussion of

thiol-redox status speaks of the expression or activity of factors important for cell-cycle progression. It does not teach or suggest that maintaining a decreased $[GSH]^2/[GSSG]$ ratio for 15 to 75 hours will cause apoptosis of malignant cells.

Ali-Osman also discusses BSO and the examiner concedes that Ali-Osman states that BSO has no effect on cell survival, though it may sensitize cell lines to treatment with carmustine. Nagendra teaches only the known fact that disulfiram decreases [GSH] and perturbs $[GSH]^2/[GSSG]$ redox status. It states that this induces oxidative stress on the brain. However, there is no suggestion that disulfiram would be useful as an anticancer agent and there is no suggestion of the features of the present invention.

The examiner's conclusion is that the skilled artisan would have a reasonable expectation that administering disulfiram would be an effective treatment for tumors, while administration of BSO would result in desensitization of tumors to carmustine treatment. The examiner further states that modifying the administration regimens, doses, length of administration, etc., in order to elicit optimal treatment of tumors is well within the purview of the skilled artisan. However, as discussed above, the crux of the present invention is administering the combination of agents in such a manner as

to cause a decrease in the $[GSH]^2/[GSSG]$ ratio to be reached and maintained in the malignant cells continuously for about 15 to about 75 hours to thereby cause apoptosis of the cancer cells. This is a critical feature of the present invention that the examiner seems to think is mere optimization. However, it is not mere optimization, as the four references relied upon by the examiner either alone or in combination, do not teach the mechanism of action that is required by the present claims.

In Ali-Osman, the only reference that talks about carmustine (BCNU), it is used in a completely different way and in a much higher concentration than is necessary in order to inhibit glutathione reductase. At the concentration disclosed by Ali-Osman, carmustine, being a mustard gas, will non-selectively kill the normal as well as the cancer cells. The present invention relies on a different characteristic of carmustine, namely that it inhibits the GR enzyme, even at low, non-toxic concentrations. Thus, Ali-Osman would not make obvious the required dosages and mode of administration as required by the present invention to allow the reduced $[GSH]^2/[GSSG]$ ratio for 15 to 75 hours.

Nagendra has nothing whatsoever to do with tumor cells. It would not provide any motivation to anyone of ordinary skill in the art reading the other references to

treat tumor cells in the manner required by the present claims.

While modifying administration regimes and doses is within the purview of the skilled artisan, this must be done within the teachings of the prior art. The present invention requires one of ordinary skill in the art to choose administration regimens, doses, length of administration, etc., in order to optimize the reduction of $[GSH]^2/[GSSG]$ for 15 to 75 hours. In the references cited by the examiner, any modification would be for completely different purposes and there would be no reason to believe that it would be obvious to happen on those modes of administration, doses, and lengths of administration that will allow the effect of the present invention and the selective effects of the killing of cancer cells as shown in the attached declarations. For all of these reasons reconsideration and withdrawal of this rejection are resoectfully urged.

Claims 1, 4, 7, 8 and 10-25 have been provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 9-20 and 25-28 of co-pending application no. 11/596,043. The examiner states that the claims are not patentably distinct. This rejection is respectfully traversed.

The claims of application no. 11/596,043 have not yet been examined. Thus, it is premature to determine whether or not any allowable claims of the present application would be directed to the same invention as any allowable claims of the '043 application. Accordingly, it is requested that the present rejection be held in abeyance until allowable subject matter is found in this case, in accordance with 37 CFR 1.111(b).

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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